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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHWADRON, RONALD B	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,530	KLIMPEL ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,30,31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

1. Claims 1-6,30-31 are under consideration.

2. The rejection of claims 29,30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons elaborated in the previous Office Action, sections 5 a) and 5 b) are withdrawn in view of the cancellation of claim 29 and amending of claim 30.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-6,29,31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Leppla et al. (WO 94/18332) in view of Noteborn et al. (WO 95/03414) for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Leppla et al. teach anthrax protective antigen (see last paragraph page 25 and first paragraph, page 26) and a fusion protein containing the PA binding domain of LF/toxin, wherein toxins are commonly full length proteins(see last paragraph page 25 and second paragraph, page 26). Leppla et al. teach that the fusion protein can contain the

first 1-254 amino acids of LF (e.g. PA binding domain)(see pages 6 and 7). The name anthrax as used by Leppla et al. refers to Bacillus anthracis (see last paragraph page 3, continued on next page). Processed protective antigen is created when the anthrax protective antigen is administered in vivo. Leppla et al. teach that the toxin/fusion protein and PA are administered as a pharmaceutical composition (see page 27) containing saline (aqueous solution of physiologically compatible salts, see page 28). Leppla et al. do not teach the conjugate contains a viral protein. Noteborn et al. teach the intracellular viral protein VP3 which can be used to kill tumor cells and other target cells (see page 8, third paragraph and page 2, last paragraph). Noteborn et al. teach immunoconjugates containing VP3 and a ligand that can be internalized by a cell (see page 9, third paragraph). The PA/PA binding domain of LF/toxin conjugate is internalized by a cell(see Leppala et al., page 4, last paragraph, continued on page 5). Leppala et al. teach the use of the aforementioned two component system to deliver a molecule into a cell (see claim 19 and 20). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Leppla teach the claimed invention except for use of a viral protein whilst Noteborn et al. teach immunoconjugates containing the viral toxin VP3 and a ligand that can be internalized by a cell and Leppla et al. teach the use of the aforementioned two component system to deliver a molecule into a cell. The recitation of an intended use in this product claim carries no patentable weight because the claimed product is the same as the product rendered obvious in the instant rejection. The dosage recited in the claims (as per defined in page 20, penultimate paragraph of the specification) is encompassed by the dose range disclosed in page 27, lines 24-25 of Leppla et al. While Leppla et al. do not teach the molar ratio recited in claim 31, Leppla et al. teach that the amount of PA and LF/fusion protein will be optimized using routine procedures. One of ordinary skill in the art would have been motivated to do the aformentioned because Leppala et al. teach the use of the aforementioned two component system to deliver a molecule into a cell and Noteborn et al. teach immunoconjugates containing VP3 and a ligand that can be internalized by a cell.

Regarding applicants comments and the Leppla declaration, the recitation of an intended use carries no patentable weight in the instant product claims. In addition, the product rendered obvious in the instant rejection would have the same properties as the claimed invention because it is structurally identical to the claimed product. It is also noted that the motivation for producing the claimed product can be different from applicants as long as the same product is produced (see MPEP 2144).

Regarding the size of the toxin molecule used in the fusion protein, Leppla et al. teach anthrax protective antigen (see last paragraph page 25 and first paragraph, page 26) and a fusion protein containing the PA binding domain of LF/toxin, wherein toxins are commonly full length proteins(see last paragraph page 25 and second paragraph, page 26). Leppla et al., page 26, second paragraph teaches uses of a toxin in the aformentioned fusion protein wherein toxin refers to a full length toxin. Said paragraph also refers to other full length proteins such as growth factors. Regarding applicants comments about Noteborn et al. said reference is cited for the use of VP3 viral toxin in the claimed conjugate. One of ordinary skill in the art would have been motivated to do the aformentioned because Leppla et al. teach the use of the aforementioned two component system to deliver a molecule into a cell and Noteborn et al. teach immunoconjugates containing VP3 and a ligand that can be internalized by a cell. Regarding applicants comments about paragraph 10 of the Leppla declaration, as per above, the motivation to produce the claimed invention cited in the instant rejection need not be the same as applicants as long as it leads to a product which is structurally the same as the claimed product.

Regarding paragraph 11 of the Leppla declaration, the instant fusion protein would have the functional properties recited in claim 1 because the product is the same as the claimed invention. Whether the product rendered obvious in the instant rejection would also eventually kill the cell or generate a Class II mediated antibody response is irrelevant, because there is currently no limitation in the claims which prohibits either of the aforementioned activities. There is no evidence that the product rendered obvious in the instant rejection would not induce a MHC class I mediated CTL response. In fact, according to the Leppla declaration, it should induce a class I response because it would be targeted to the appropriate anatomic compartment for processing. Furthermore, it appears that paragraph 11 of the Leppla declaration indicates that the conjugate would be unable to kill cells because the toxic protein moiety would be processed. However, this is clearly inaccurate because both native APABP and the conjugates disclosed in Leppla et al. are cytotoxic. Furthermore, the VP3 protein disclosed by Noteborn et al. is both immunogenic and cytotoxic. The instant rejection discloses why it is obvious to create a product that is structurally identical to the claimed invention.

Regarding applicants comments about "processed PA", the rejection refers to the processed PA of claim 2 (A.K.A. cleaved PA which reveals the LF binding site).

Regarding applicants comments that Leppala et al. do not disclose use of a viral protein in their conjugate, this issue is addressed by the addition of the Noteborn et al. (WO

95/03414) reference. Regarding applicants comments about dosage, the specification discloses on page 20 that:

For each recipient, the total vaccine amount necessary can be deduced from protocols for immunization with other vaccines. The exact amount of such antigen- APABP and PA compositions required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the particular fusion protein used, its mode of administration, and the like. Generally, dosage will approximate that which is typical for the administration of other vaccines, and will preferably be in the range of about 10 ng/kg to 1 mg/kg.

Thus, regarding the functional dosage recited in the claims, said dosage will vary according to the antigen and particular parameters as per stated above. Said passage also discloses a general range of antigen to be used. Leppla et al., disclose administration of the instant invention at a dosage that overlaps that encompassed by the limitation now recited in the claims (see page 27, lines 24-25).

The recitation of an intended use carries no patentable weight in the instant product claims. In addition, because it is structurally identical to the claimed product, it would have the same properties as the claimed product. Furthermore, the claimed composition as disclosed in Leppala et al. could induce a CTL response depending on the recipient and the protein used. For example, virtually any protein would be immunogenic/induce CTL if administered into another species (eg. the art recognizes that mouse Ig is immunogenic when administered to humans, etc). The invention rendered obvious in the instant rejection has the same structure as the claimed invention and would therefore have the same properties as the claimed invention. Regarding applicants comments that the viral protein recited in the claims would not kill the target, there is no limitation in the claims that the protein is not toxic to the cell. The CAV proteins disclosed by Noteborn are both cytotoxic and immunogenic (see claim 1). One of ordinary skill in the art would have been motivated to do the aformentioned because Leppala et al. teach the use of the aforementioned two component system to deliver a molecule into a cell and Noteborn et al. teach immunoconjugates containing VP3 and a ligand that can be internalized by a cell.

5. Claims 1-6,30,31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Milne et al. (Mol. Microbiology 15:651, 1995) in view of Arora et al. (J. Biol. Chemistry 268:3334), Leppla et al. (WO 94/18332) , EP 0 532 090A2 (issued March 3, 1991) and Donnelly et al . (PNAS 90:3530:1993).

Milne et al. teach a composition comprising anthrax protective antigen (PA) and an antigen bound to anthrax protective antigen binding protein (APABP) (See Figure 3, in particular). Anthrax toxin lethal factor (LF) is the APABP. The composition taught by Milne et al. comprises diphtheria toxin (the antigen) bound to residues 1-255 of lethal factor of Bacillus anthracis. Milne et al. teach that LF binds to anthrax protective antigen (PA) (see abstract). Milne et al. teach that an embodiment of the diphtheria toxin-LF fusion protein in which the diphtheria toxin has a mutation that reduces the cytotoxicity of the diphtheria toxin (see pages 663, second column, in particular). Milne et al. further teach that anthrax toxin represents a model for design of a protein translocation system to deliver heterologous proteins to the cytoplasm of mammalian cells. In this system PA would co-ordinate the entry of a fusion protein into the mammalian cells. Milne et al. further teach that heterologous protein may be bound to the amino or carboxyl-terminus of LF fragment and that the relatively small size of the LF fragment and its ability to be expressed at high levels in E.coli make it an ideal candidate for the construction of fusion proteins (see page 664, in particular) . Milne et al. teach that native PA is processed to 63kDa protein which binds to the cell surface of mammalian cells and that the processed 63kDa PA has a binding site to which LF binds. (see page 661, second column in particular). Milne et al. do not teach that the conjugate contains a viral protein or HIV protein.

Arora et al. teach that the PA- binding domain of anthrax lethal toxin lies within residues 1-254 (see abstract, in particular). Arora et al. teach fusion proteins comprising anthrax protective antigen binding protein (IE LF) could be used to present peptides to the MHC Class I antigen recognition system (see page 3340, in particular). Arora et al. also teach the domains I and II Pseudomonas exotoxin A has been used to internalize proteins bound to the exotoxin. Arora et al. teach than in addition to their potential as cytotoxic agents such fusion proteins could be used to present peptides to the major histocompatibility class I antigen recognition system and that anthrax toxin could also be used for such a function. Arora et al. also disclose that the attachment of large polypeptide to LF does not affect the ability of the fusion protein to be internalized via PA63 domain (see page 3340, second column, in particular). Leppla et al. teach anthrax protective antigen (see last paragraph page 25 and first paragraph, page 26) and a fusion protein containing the PA binding domain of LF/toxin, wherein toxins are commonly full length proteins(see last paragraph page 25 and second paragraph, page 26). Leppla et al. teach that the fusion protein can contain the first 1-254 amino acids of LF (e.g. PA binding domain)(see pages 6 and 7). The name anthrax as used by Leppla et al. refers to Bacillus anthracis (see last paragraph page 3, continued on next page).

Processed protective antigen is created when the anthrax protective antigen is administered in vivo. Leppla et al. teach that the toxin/fusion protein and PA are administered as a pharmaceutical composition (see page 27) containing saline (aqueous solution of physiologically compatible salts, see page 28). While Leppla et al. do not teach the molar ratio recited in claim 31, Leppla et al. teach that the amount of PA and LF/fusion protein will be optimized using routine procedures.

EPO 532090 A2 discloses a fusion protein comprising a bacteria toxin that has a translocation domain bound to an antigen and further comprises a cellular recognition domain. EP 0532090 A2 discloses a hybrid protein comprising a bacteria toxin that has a translocation domain bound to an polypeptide or protein and a recognition domain. EP 0532 090 A discloses that such a protein is capable of eliciting an immune response by cytotoxic T lymphocytes against HIV protein in the context of HLA-A2 (an MHC class I allele) and may be used as a vaccine for peptide bound to the translocation domain (See claims, 1-9 and 18-31 and page 15 lines 35-41, in particular). EP0 532 090A2 further teaches that the vaccine may be prepared in sterile water, sterile saline (which comprises physiologically compatible salts).

Donnelly et al. teach that one approach to inducing an immune response (CTL) to a protein has been the delivery of foreign proteins to the cytosol through use of replicating vectors, IE viruses. Donnelly et al. further teach that immunization with exogenous proteins generally results in endocytosis of the antigens leading to their process for presentation in association with MHC class II rather than with class I (see page 3530, in particular). Donnelly et al. further teach that delivering exogenous protein antigens into intracellular compartments under physiologic conditions would be useful for developing CTL vaccines and that bacterial toxins which reach the cytosol by means of translocation through endosomal membrane may be used to deliver peptides or proteins into cells. Donnelly et al. also teach the toxin-protein fusion protein could comprise entire proteins and that the such a fusion protein could be used as a vaccine to elicit an immune response to the protein (see page 3533, in particular). Donnelly et al. teach a fusion protein comprising a truncated Pseudomonas aerugionosa exotoxin A which consists of its binding and translocation domains and an antigenic peptide (see Figure 1 and 3532-3533, in particular).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Milne et al., Leppla et al. and Arora et al. disclose that a composition comprising anthrax protective antigen (PA) and an antigen bound to anthrax protective antigen binding protein (APABP) can used to deliver the target molecule to the cytosol, Arora

et al. teach than in addition to their potential as cytotoxic agents such fusion proteins could be used to present peptides to the major histocompatibility class I antigen recognition system and that anthrax toxin could also be used for such a function whilst EP 0531090 A discloses a hybrid protein comprising a bacteria toxin that has a translocation domain bound to an polypeptide or protein and a recognition domain and that such a protein is capable of eliciting an immune response by cytotoxic T lymphocytes against HIV protein in the context of HLA-A2 (an MHC class I allele) and Donnelly et al. teach a fusion protein comprising a truncated bacterial toxin which consists of its binding and translocation domains and an antigenic peptide (see Figure 1 and 3532-3533, in particular). One of ordinary skill in the art at the time of the invention would have been motivated to use LF domain taught by Aurora et al. in the fusion protein since Aurora et al. teaches that toxins such as anthrax LF and the domains I and II Pseudomonas exotoxin A have been used to internalize proteins bound to the exotoxin. Aurora et al. teaches that PA binds to cells and serves as a receptor for LF-protein fusion proteins which facilitates translocation of the LF-proteins fusion protein into the cytoplasm. Donnelly et al. and Aurora et al. teach internalization of the antigen induces CTL responses to the antigen. One with ordinary skill in the art would have been motivated to use whole proteins are fragments of proteins in the fusion protein since Aurora et al. teaches that large proteins bound to the anthrax LF do not affect its ability to translocate the fusion protein into the cytoplasm and Donnelly et al. also teach the toxin-antigen fusion protein could comprise entire proteins and that the such a fusion protein could be used as a vaccine to elicit an immune response to the protein

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached Monday to Thursday from 7:30am to 6:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571-2720841. The fax phone number for the organization where this application or proceeding is assigned is 703-

872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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